Bilaterally Positive Biopsy Cores Are Associated with Non-Organ-Confined Disease in Prostate Cancer Patients Eligible for Active Surveillance

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Bilaterally Positive Biopsy Cores Are Associated with Non-Organ-Confined Disease in Prostate Cancer Patients Eligible for Active Surveillance

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Key Words

Active surveillance · Patient selection · Laterality of prostate cancer-positive cores · Non-organ-confined disease

Abstract

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Introduction

Screening for prostate cancer (PCa) has been shown to reduce disease-specific mortality [1]; it is, however, associated with significant overtreatment due to the detection of many indolent tumors (i.e. tumors which would never become clinically manifest and which would never harm the patient even if left untreated) [2]. In an effort to reduce this overtreatment, more and more PCa patients are included in active surveillance (AS) programs. Candidates for this strategy are patients who are most likely to harbor insignificant (i.e. low-volume, non-aggressive PCa) disease. Available evidence suggests that this strategy is a viable alternative to immediate treatment [3, 4]. However, underestimation of the

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Table 1. Patient characteristics

	Overall	Unilateral	Bilateral	Significance
Number of patients	161	144	17	
Age at operation, mean/median (range)	62/63 (43–76)	62/63 (43–76)	62/64 (49–72)	0.91*
PSA at operation, mean/median (range)	5.2/5 (0.6–9.2)	5.2/5 (0.6–9.2)	5.1/5 (2.6–8.6)	0.84*
Number of biopsy cores taken, mean/median (range)	8.7/8 (4–14)	8.7/8 (4–14)	8.5/8 (8–13)	0.74*
Biopsy Gleason score, number of patients				
<6	24 (15%)	20 (14%)	4 (24%)	0.29**
6	137 (85%)	124 (86%)	13 (76%)	
Final Gleason score, number of patients				
<7	105 (65%)	96 (67%)	9 (53%)	0.26**
≥7	56 (35%)	48 (33%)	8 (47%)	

Overview over the main patient characteristics in the overall group and the subgroups of patients with unilaterally or bilaterally PCa-positive biopsy cores. Significance was tested using t test for continuous and Pearson's χ^2 test for categorical variables. * t test; ** Pearson's χ^2 test.

tumor burden and subsequent undertreatment of significant PCa is an obvious concern of the AS strategy. Additional parameters to predict indolent PCa more accurately would therefore be desirable, as long as they are specific enough not to falsely exclude too many indolent cancers. In the absence of more reliable predictors, the number of PCa-positive biopsy cores and the extent of PCa in the respective cores are most often used as surrogate parameters for tumor volume. Current AS protocols accept up to one positive biopsy core out of three cores taken as an inclusion criterion [5]. Patients with up to two positive biopsy cores are accepted in the vast majority of AS cohorts, regardless of the distance between the two positive cores [4, 6]. Indeed, this distance is very difficult to ascertain in clinical practice and is therefore generally not useful as an additional proxy parameter for tumor volume. It is, however, conceivable that a patient with one positive core from each side of the prostate has on average a larger tumor volume than a patient with positive biopsies only from one side of the prostate. The goal of this study was to evaluate whether non-organ-confined disease is more prevalent if a prostate biopsy is positive bilaterally versus only unilaterally among patients eligible for AS.

Patients and Methods

We retrospectively investigated the data of all patients who underwent radical prostatectomy at the University Hospital of Zurich, Switzerland, from 1999 to 2009 and fulfilled our current AS inclusion criteria (clinically organ-confined disease, PSA <10 ng/ml, no Gleason pattern 4 or 5, ≤2 positive biopsy cores) at the time of surgery. In these patients, the location of PCa-positive biopsy cores (unilateral versus bilateral) was associated with the final pathology results. This study was conducted in accordance with the local ethical rules for retrospective studies.

The primary outcome was the odds and odds ratio (as a measure of the relative risk) of having non-organ-confined disease between patients with only one PCa-affected prostatic lobe (unilateral disease, irrespective of whether one or two biopsy cores were affected by PCa) and patients with bilaterally positive biopsies (one cancer-positive biopsy core on each side). The secondary outcome was the odds and odds ratio (as a measure of the relative risk) in the subset of patients with two PCa-affected biopsy cores, comparing bilaterally PCa-positive patients (one PCa-positive biopsy core in each prostatic lobe) against unilateral PCa-positive patients (two PCa-positive cores within one prostatic lobe).

Statistical Analysis

Nominal variables were compared using Fisher's exact test and continuous variables using Mann-Whitney test. Odds ratios including 95% Wald confidence intervals (CIs) computed on the logit scale are provided where suitable. Probabilities were estimated by calculating relative frequencies. The estimated proportions were completed with a 95% Wilson CI. All tests were performed at a significance level of $\alpha = 0.05$ and CIs were computed using a confidence level of 95%. All analyses were done using the R statistical software (R Development Core Team, 2012).

Results

We identified 165 patients fulfilling our AS criteria at the time of radical prostatectomy. Complete information with regard to the location of cancer-positive biopsy cores was available in 161 patients; these 161 patients were included in the analysis. Out of these 161 patients, 144 had unilaterally PCa-positive biopsy cores; the remaining

Table 2. Preoperative biopsy results versus postoperative pT status in the overall group

Preoperative biopsy findings	Final stage pT				Comparison	
	≤pT2	>pT2	total	proportion of >pT2	p	odds ratio (95% CI)
Biopsy side						
Unilateral	142	2	144	1%	0.009	14.67 (1.55–189.23)
Bilateral	14	3	17	18%		
Total	156	5	161	3%		

Cross tabulation of preoperative biopsy results concerning laterality of PCa-positive cores versus postoperative final PCa stage in the overall group. Indicated is the number of patients, the proportions, the p value (Fisher's exact test) as well as the odds ratio with 95% confidence interval.

Table 3. Preoperative biopsy results versus postoperative pT status in the subgroup of patients with two positive biopsy cores

Preoperative biopsy findings	Final stage pT				Comparison	
	≤pT2	>pT2	total	proportion of >pT2	p	odds ratio (95% CI)
Biopsy side						
Unilateral	40	0	40	0%	0.02	(∞)
Bilateral	14	3	17	18%		
Total	54	3	57	5%		

Cross tabulation of preoperative biopsy results concerning laterality of PCa-positive cores versus postoperative final PCa stage in patients with two PCa-positive biopsy cores preoperatively. Indicated is the number of patients, the proportions, the p value (Fisher's exact test) as well as the odds ratio with 95% confidence interval. Due to zero false-negative observations the odds ratio reaches infinity.

17 patients had bilaterally PCa-positive biopsy cores. The main patient characteristics of the overall group and the subgroups are summarized in table 1.

Further, out of these 161 patients, 5 (3%) had >pT2 (non-organ-confined) disease on final pathology. Only 2 out of the 144 patients with unilaterally positive biopsy cores had >pT2 disease, representing a proportion of 1% (95% CI 0.00–0.05), whereas 3 out of the 17 patients with bilaterally positive biopsy cores had >pT2 disease, representing a proportion of 18% (95% CI 0.06–0.41) (table 2). Comparison with respect to laterality of PCa-positive biopsy cores showed a high statistical significance (p = 0.009). The estimated odds ratio for non-organ-confined disease in bilaterally positive patients compared to unilaterally positive patients was 14.67 (95% CI 1.55–189.23). Out of the subset of 57 patients with two PCa-affected biopsy cores, 3 (5%) had >pT2 disease on final pathology. Here, none of 40 patients with unilaterally PCa-positive biopsy cores had >pT2 disease, representing a proportion of 0% (95% CI 0.00–0.09), whereas 3 out of 17 patients with bilaterally PCa-positive biopsy cores had >pT2 disease, representing a proportion of 18% (95% CI 0.06–0.41). The calculation of the odds ratio reached infinity due to zero false-negative observations. The comparison with respect to laterality of PCa-positive biopsy cores was statistically significant (p = 0.02) (table 3).

Adding laterality of positive biopsy cores as a further inclusion or exclusion criterion to our AS protocol ended in a moderate to good sensitivity of 60% (3 out of 5), a very good specificity of 91% (142 out of 156) as well as a high overall accuracy of 90% (145 out of 161) for the iden-

tification of non-organ-confined PCa. Sensitivity, specificity and accuracy in the subset of patients with two PCa-positive biopsy cores only were 100% (3 out of 3), 74% (40 out of 54) and 75% (43 out of 57), respectively.

Discussion

In this study, we evaluated whether non-organ-confined disease is more prevalent if a prostate biopsy is positive bilaterally versus only unilaterally among patients otherwise eligible for AS according to common AS protocols. We showed that patients with bilaterally positive prostate biopsy cores compared to patients with only unilaterally affected cores are indeed at a statistically significantly higher risk of harboring locally advanced disease whereby the odds (as an estimate of risk) for non-organ-confined disease are 14.67 times greater in bilaterally positive patients compared to unilaterally positive patients.

Accurate risk stratification at the time of PCa diagnosis is crucial for an optimal treatment choice maintaining the right balance between adequate cancer control on the one side and therapy-related side effects on the other. Hence, additional parameters predicting indolent PCa more accurately are very desirable in order to make the AS strategy as safe as reasonably possible. However, such additional parameters need to be specific enough not to exclude a significant number of patients from the AS strategy by mistake. The laterality of PCa-positive biopsy cores (unilaterally versus bilaterally positive cores) as an additional selection parameter for AS patients showed this specific characteristic within our study. Whereas 60% of all non-organ-confined PCa cases could have been predicted, the vast majority (about 90%) of the initially selected men would still have qualified for AS. In comparison, using a different PSA cut-off value to detect non-organ-confined disease with the same sensitivity as the laterality variable would need a lowering of the cut-off point to 5.6 ng/ml. This would be accompanied by a specificity of 61%, representing a 30% absolute difference compared to the specificity of the laterality variable. Hence, due to this high specificity of the laterality variable, bilaterally positive biopsies may represent a reasonable exclusion criterion for AS. However, due to the limitations of our study the results must be corroborated in further studies.

Formerly, Raventós et al. [7] also reported about the predictive ability of laterality (unilateral versus bilateral) of PCa-affected biopsy cores in the prediction of pathologically insignificant PCa as defined by tumor volume $<0.5\ cm^3$ and Gleason score ≤6 in radical prostatectomy specimens. They used a retrospective study design in a group of 280 patients; 108 patients (38.3%) were at low risk amongst the criteria of D'Amico [8] (PSA ≤10 ng/ml and Gleason Score <7 and cT1–2a) at the time of surgery. The association with laterality was observed in the overall group as well as in the low-risk group. Focusing on the low-risk group, the percentage of patients with bilaterally positive biopsy cores was only 4.3% in the group of patients with insignificant disease in final pathological findings, whereas the percentage was 26.2% in the group with significant disease in final pathological findings ($p = 0.024$). However, in logistic regression the predictive ability of laterality disappeared whereas the number of positive cores remained as a predictive variable. Our study design is in analogy to the one of Raventós et al.; however, there are two main differences. First, our study population was different and much more specifically defined according to our current AS criteria. Thus, the low-risk group in the study of Raventós et al. was older on average (mean age 65.2 years, range 36.1–76.2) and had higher PSA values (mean 6.6 ng/ml, range 4.1–9.7). The overall number of biopsy cores taken was not specified for the low-risk group, the mean and median of total cores taken in the overall group, however, were 7.4 and 6. The number of positive cores in the low-risk group ranged from 1 to 7, whereas in our cohort none of the patients had more than two positive biopsy cores. Second, our outcome was much more specific and focused on tumor volume assessment. This is crucial since we assume that the variable laterality fits with tumor volume and not tumor aggressiveness, hence a combined outcome as used by Raventós et al. may be suboptimal. These differences in study population and outcome definition could be crucial when comparing the results from our study to the one of Raventós et al.

Several aspects of our study require discussion. This is a retrospective analysis performed within a group of patients after radical prostatectomy fulfilling all criteria for AS at the time of surgery. Obviously, the data set was originally not designed to answer our specific research question. Hence, the number of patients, or the number of observations, respectively, is relatively low. This also becomes evident in the broad 95% CI, reflecting the uncertainty due to the small number of observations. However, the very low rate of non-organ-confined disease (>pT2) in our cohort underscores how effective our selection criteria for AS patients already are. The fact that a very simple additional selection parameter shows a specificity of

>90% in this scenario is in itself remarkable. Moreover, it may be that our retrospective study cohort is not representative; however, it is not a selection, but rather a consecutive subset of patients out of a consecutive radical prostatectomy cohort between 1999 and 2009 fulfilling our current AS criteria at the time of surgery.

An additional limitation of our study is that data about the amount of cancer involvement (usually indicated as percentage) within a PCa-affected biopsy core were unavailable within our data set; this criterion was shown to be very useful as a surrogate in the assessment of the real cancer volume. However, since this is a retrospective analysis, we have to take into consideration that historically the percentage of cancer-affected volume within one biopsy core was not routinely associated with an indication of biopsy core length; hence, the pure evaluation of percentage of cancer involvement per core would have been a difficult parameter within this cohort anyhow. Four patients (2%) had missing data, so that only 161 out of 165 patients were entered into our analysis.

Furthermore, it may be that the two groups (unilaterally versus bilaterally cancer-positive biopsy cores) differed in other variables than the laterality of positive biopsy cores and that this led to confounding. However, we found no statistically significant differences in important patient characteristics as shown in table 1; a more sophisticated comparison using additionally PSA density as well as the assessment of the association with real tumor volume in the final pathology specimen was not possible due to unavailable corresponding data in our data set. Further, due to very few patients with biopsy core sample numbers below 8 (n = 7; 4 patients with 6 biopsy cores, 1 patient with 5 biopsy cores and 2 patients with 4 biopsy cores only) we may reasonably assume that the group of patients with unilaterally PCa-positive biopsy cores is not undersampled compared to the group of patients with bilaterally PCa-positive biopsy cores. However, we lack the information about why these unusually low numbers of biopsy cores were taken during the diagnostic work-up. At our institution, in earlier years an 8–12- and currently a 12-core biopsy protocol is standard in the diagnostic work-up; however, we did not perform a confirmation biopsy in all of the patients with an out-of-hospital diagnosis of PCa by a low number of biopsy cores sent to our department for treatment. In the end, the population under investigation already represents a very well-defined subset of PCa patients, which decreases the potential for confounding upfront.

Lastly, for our primary outcome we compared men with two positive biopsy cores (one on each side of the prostate) to men with either one or two positive biopsy cores (just on one side). Thus, it could be argued that our results simply reflect the comparison of different numbers of positive cores rather than laterality of the positive cores. However, the effect remained statistically significant even in the subgroup analysis of only patients with two positive cores. However, due to zero false-negative observations the size of the effect could not be assessed in this subgroup, nor could we do a meaningful regression analysis adjusting for the number of positive cores due to the limited number of observations. A larger number of patients will be needed to assess the amount of the effect and to narrow the CIs and as such to improve the accuracy of the results.

In summary, using the variable laterality as an additional criterion to our current AS criteria results in a moderate to good sensitivity for identifying non-organ-confined disease on final pathological findings upfront and reduces undertreatment – an obvious concern in AS patients – by decreasing misclassification in our cohort relatively by 60% (2 compared to 5 misclassified men) and absolutely by 2% (2 compared to 5 misclassified men out of 161). The fact that the rate of non-organ-confined and as such misclassified disease cases (>pT2) in our cohort is already very low with only 3% makes the additional obvious improvement by adding one very simple additional selection parameter indeed remarkable, especially since the corresponding specificity remains over 90%. Nevertheless, the prize to pay for this additional safety is the finally unnecessary exclusion of men who actually would qualify for AS due to decrease – even only slightly – in specificity (minus 9%); this in turn results in overtreatment. However, in our cohort overall only two men would have been affected hereby, representing relatively as well as absolutely a little more than 1% of all men in our cohort. Hence, by applying the additional parameter laterality to our current AS criteria, the relation between risk reduction of undertreatment and overtreatment seems beneficial for its use. Taking all the limitations of our study into account and against the background that currently various protocols for AS inclusion and exclusion exist, we understand our findings much more as a hint than proof for the usefulness of the bilaterality variable in AS.

In conclusion, in our study of PCa patients eligible for AS amongst our current criteria, patients with bilaterally positive biopsy cores were significantly more likely to harbor a non-organ-confined tumor than patients with unilaterally positive cores only. Laterality of positive biopsy cores showed a very good specificity of 91% for the

identification of non-organ-confined PCa. Due to this high specificity, bilaterally positive biopsies may represent a reasonable exclusion criterion for AS if our results are corroborated in further studies.

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Disclosure Statement

The authors indicated no potential conflicts of interest.

Author Contributions

Concept and design: M. Müntener. Administrative support: S. Gfeller. Provision of study materials or patients: M. Müntener, T. Sulser. Collection and assembly of data: S. Gfeller, M. Müntener, R.A. Largo, M. Tremp. Data analysis and interpretation: M. Paul, M. Müntener, C. Poyet, M.H. Umbehr. Manuscript writing: all authors.

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